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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/708,506	11/09/2000	Arno Hartmann	MERCK-2056	2626

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/708,506	HARTMANN ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,16-18,24,25,27,30,32 and 35-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,16-18,24,25,30,32 and 35-40* is/are rejected.

7)☒ Claim(s) *27 and 41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Due to the necessity of addressing new grounds of rejection, the finality of the previous Office Action (20 January 2006) is hereby withdrawn in view of substantial new issues, as set forth below.

Status of Application, Amendments and/or Claims

The amendment filed 20 April 2006 (Paper No.) has been entered in full. Claims 1, 5-15, 19-23, 26, 28, 29, 31, 33, 34 are cancelled. Claims 2-4, 16-18, 24, 25, 27, 30, 32, 35-41 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejection to claims 2-4, 16-18, 24, 25, 27, 30, 32, 33, 35-41 under 35 U.S.C. 112, first paragraph, written description (new matter), as set forth at pages 3-4 of the previous Office Action (20 January 2006) is *withdrawn* in view of the amendment (20 April 2006).

The rejection to claims 2-4, 16-18, 24, 25, 27, 30, 32, 33, 35-41 under 35 U.S.C. 112, first paragraph, enablement, as set forth at pages 4-5 of the previous Office Action (20 January 2006) is *withdrawn* in view of Applicant's arguments (20 April 2006).

The rejection to claims 2-4 and 30 under 35 U.S.C. 112, second paragraph, as set forth at pages 5-6 of the previous Office Action (20 January 2006) is *withdrawn* in view of the amendment (20 April 2006).

Claim Rejections - 35 USC § 103(a)

Claims 2-4, 16-18, 24, 25, 30, 32, 35 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sytkowski *et al.* WO 99/02709 (reference of record) in view of Cox, III, U.S. Patent 6,608,183 B1 (reference of record) and Okasinski *et al.,* US Patent No. 5,888,772 (reference of record).

Sytkowski *et al.* teach a fusion protein comprising an Fc portion of an Ig molecule and human erythropoietin (EPO) portion, wherein the Fc portion is fused covalently via its C-terminus directly or indirectly to the EPO portion (page 3, lines 6-31; page 16, lines 31-33 and column 14, lines 21-32)(**applies to claims 30, 32**). Sytkowski *et al.* teach that EPO fusion proteins comprising immunoglobulin polypeptide chains will have increased biological activity and increased *in vivo* half-life compared to wildtype (page 2, lines 10-30; page 4, lines 12-18; page 5, lines 5-10 and page 19, line 8-page 21, line 8). Exemplary EPO molecules include mutant EPO with increased biology (page 5, lines 1-15 and page 8, line 17-page 12, line 22)(**applies to claims 2-4**). Sytkowski *et al.* teach that the entire immunoglobulin heavy chain constant region can be fused to the EPO molecule (page 15, lines 14-15)(**applies to claim 16**). Sytkowski *et al.* teach the use of human Fc (page 23, line 20)(**applies to claims 17, 18**). Sytkowski *et al.* teach pharmaceutical compositions comprising the EPO fusion protein (page 21, lines 9-31)

(**applies to claims 24, 25**). Sytkowski *et al.* teach wherein the Fc portion is mutated or truncated (page 5, lines 11-20 and page 13, line 22-page 14, line 31) (**applies to claim 35**). Sytkowski *et al.* teach linkers (page 17, lines 5-16) (**applies to claim 39**). Sytkowski *et al.* do not teach EPO variants wherein Trp at position 88 is substituted with a cysteine residues or wherein EPO comprises a Cys29-Cys88 disulfide bond.

Cox teach III, U.S. Patent 6,608,183 B1 teaches human EPO variants wherein amino acids are substituted with cysteines. Cox teaches the substitution of Trp at position 88 for a cysteine amino acid (column 23, lines 15-42 and column 26, lines 27-51)(**applies to claims 30**). Cox teaches that in wildtype EPO, cysteines are located in amino acids positions 29 and 33 (lines 51-57)(**applies to claim 30**).

Okasinski *et al.* teach that human EPO variants wherein a cysteine at position 33 is replaced with another amino acid will result in improved *in vivo* activity (column 5, lines 1-9; column 6, lines 19-27; column 18, lines 64-67 and column 21, lines 43-46). Okasinski *et al.* teach EPO proteins which have a pattern of disulfide bonding distinct from human or mammalian erythropoietin, wherein the new engineered cysteine residues form a disulfide bond (column 24, lines 17-55 and Figure 4) (**applies to claim 30**).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the fusion protein comprising an Fc portion of an Ig molecule and human EPO as suggested by Sytkowski *et al.* with cytokine substitutions in EPO as suggested by Cox and Okasinski *et al.* with a reasonable expectation of success. The motivation and expected success is provided by Sytkowski, Cox and

Okasinski. Sytkowski *et al.* demonstrate increased biological activity and half-life when EPO is fused with an immunoglobulin and Cox and Okasinski *et al.* who demonstrate another means of increasing EPO activity by making specific cytokine substitutions or by mutating cysteine residues, respectively.

Claims 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over unpatentable over Sytkowski *et al.* WO 99/02709 in view of Cox, III, U.S. Patent 6,608,183 B1 and Okasinski *et al.,* US Patent No. 5,888,772, as applied to claim 30 above, and further in view of Bolt *et al.,* U.S. 5,585,097 (reference of record).

The teachings of Sytkowski *et al.,* Cox and Okasinski *et al.* are described above. None of the references teach mutations in Fc, wherein the asparagine at amino acid position 297 of IgG1 is mutated. Bolt *et al.,* U.S. 5,585,097 teach mutations wherein asparagine at position 297 in IgG1 is replaced with another amino acid, which results in a protein that cannot be glycosylated (column 6, lines 28-54)(**applies to claims 36-38**).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the fusion protein comprising an Fc portion of an Ig molecule and human EPO as suggested by Sytkowski *et al.* with cytokine substitutions in EPO as suggested by Cox and Okasinski *et al.* and Fc mutations in IgG1 as suggest by Bolt *et al.* with a reasonable expectation of success. The motivation and expected success is provided by Sytkowski, Cox, Okasinski *et al.* and Bolt *et al.* in that Sytkowski demonstrates increased biological activity and half-life when EPO is fused with an

immunoglobulin and Cox and Okasinski *et al.* who demonstrate another means of increasing EPO activity by making specific cytokine substitutions or by mutating cysteine residues, respectively. Bolt *et al.* teach that altering the glycosylation of IgG1 at asparagine 297 will help the antibody avoid the complement dependent cytolysis pathway.

Claims 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over unpatentable over Sytkowski *et al.* WO 99/02709 in view of Cox, III, U.S. Patent 6,608,183 B1 and Okasinski *et al.,* US Patent No. 5,888,772, as applied to claims 30 and 39 above, and further in view of Sgarlato *et al.,* US Patent No. 5,935,824. The teachings of Sytkowski *et al.,* Cox and Okasinski *et al.* are described above. None of the references teach linkers which lack a protease site. Sgarlato *et al.* teach linkers, which lack a protease site (column 39, lines 20-33).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the fusion protein comprising an Fc portion of an Ig molecule and human EPO as suggested by Sytkowski *et al.* with cytokine substitutions in EPO as suggested by Cox and Okasinski *et al.* and a linker which lacks a protease cleavage site as taught by Sgarlato *et al.* with a reasonable expectation of success. The motivation and expected success is provided by Sytkowski, Cox and Okasinski *et al.,* in that Sytkowski demonstrates increased biological activity and half-life when EPO is fused with an immunoglobulin and Cox and Okasinski *et al.* who demonstrate another means of increasing EPO activity by making specific cytokine substitutions or by

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RMD
5/30/06

Marianne P. Allen

MARIANNE P. ALLEN
PRIMARY EXAMINER

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